

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

REC'D 22 NOV 2005

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Applicant's or agent's file reference PN0369-PCT	FOR FURTHER ACTION	
	See Form PCT/IPEA/416	
International application No. PCT/NO2004/000286	International filing date (day/month/year) 28.09.2004	Priority date (day/month/year) 29.09.2003
International Patent Classification (IPC) or national classification and IPC A61K49/00		
Applicant AMERSHAM HEALTH AS		

<ol style="list-style-type: none"> This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36. This REPORT consists of a total of 9 sheets, including this cover sheet. This report is also accompanied by ANNEXES, comprising: <ol style="list-style-type: none"> <input type="checkbox"/> <i>(sent to the applicant and to the International Bureau) a total of sheets, as follows:</i> <ul style="list-style-type: none"> <input type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions). <input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box. <input type="checkbox"/> <i>(sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</i>
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<ol style="list-style-type: none"> This report contains indications relating to the following items: <ul style="list-style-type: none"> <input checked="" type="checkbox"/> Box No. I Basis of the opinion <input type="checkbox"/> Box No. II Priority <input checked="" type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability <input type="checkbox"/> Box No. IV Lack of unity of invention <input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement <input checked="" type="checkbox"/> Box No. VI Certain documents cited <input type="checkbox"/> Box No. VII Certain defects in the international application <input checked="" type="checkbox"/> Box No. VIII Certain observations on the international application

Date of submission of the demand 01.07.2005	Date of completion of this report 22.11.2005
Name and mailing address of the international preliminary examining authority:  European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Dullaart, A Telephone No. +31 70 340-



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Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

This report is based on translations from the original language into the following language, which is the language of a translation furnished for the purposes of:

international search (under Rules 12.3 and 23.1(b))

publication of the international application (under Rule 12.4)

international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on (*replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report*):

Description, Pages

1-29 as originally filed

Claims, Numbers

1-12 as originally filed

- a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. The amendments have resulted in the cancellation of:

 - the description, pages
 - the claims, Nos.
 - the drawings, sheets/figs
 - the sequence listing (*specify*):
 - any table(s) related to sequence listing (*specify*):

4. This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

 - the description, pages
 - the claims, Nos.
 - the drawings, sheets/figs
 - the sequence listing (*specify*):
 - any table(s) related to sequence listing (*specify*):

* If item 4 applies, some or all of these sheets may be marked "superseded."

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:
 - the entire international application,
 - claims Nos. 1-12 in part
 - because:
 - the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):
 - the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
 - the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
 - no international search report has been established for the said claims Nos. 1-12 in part
 - the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
 - the written form has not been furnished
 - does not comply with the standard
 - the computer readable form has not been furnished
 - does not comply with the standard
 - the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.
 - See separate sheet for further details

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Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	
	No: Claims	1-12
Inventive step (IS)	Yes: Claims	
	No: Claims	1-12
Industrial applicability (IA)	Yes: Claims	1-12
	No: Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

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Supplemental Box relating to Sequence Listing

Continuation of Box I, item 2:

1. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this report has been established on the basis of:
 - a. type of material:
 a sequence listing
 table(s) related to the sequence listing
 - b. format of material:
 in written format
 in computer readable form
 - c. time of filing/furnishing:
 contained in the international application as filed
 filed together with the international application in computer readable form
 furnished subsequently to this Authority for the purposes of search and/or examination
 received by this Authority as an amendment on
2. In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
3. Additional observations, if necessary:

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Re Item III.

In the present application, the International Searching Authority has restricted the search because of the following objections under Articles 5 and 6 PCT.

Present claims 1-12 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds prepared in the examples, and those compounds specifically mentioned in the claims.

As it is not possible to form an opinion on unsearched subject-matter, the following must be limited accordingly.

Re Item V.

1 Reference is made to the following documents:

- D1: **MALIK E et al: "Fluorescence diagnosis of endometriosis using 5-aminolevulinic acid"**
Surgical Endoscopy, Vol. 14, no. 5, 2000, pages 452-455, XP002326510 ISSN: 0930-2794
- D2: **WO 01/23005 A (SCHERING AKTIENGESELLSCHAFT; SCHIRNER, MICHAEL; LICHA, KAI; DINKELBORG) 5 April 2001 (2001-04-05)**
- D3: **US 2003/162234 A1 (JALLAD KARIM N ET AL) 28 August 2003 (2003-08-28)**
- D4: **WO 93/02192 A (REPLIGEN CORPORATION) 4 February 1993 (1993-02-04)**
- D5: **WO 03/079015 A (VISEN MEDICAL, INC; POSS, KIRTLAND, G; MADDEN, KAREN, N; JONES, ELLA;) 25 September 2003 (2003-09-25)**
- D6: **SOUKOS, N. S. ET AL: "Monoclonal antibody-tagged receptor-targeted contrast agents for detection of cancers"**
PROCEEDINGS OF SPIE-THE INTERNATIONAL SOCIETY FOR OPTICAL

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ENGINEERING , vol. 4259 (Biomarkers and Biological Spectra Imaging), pages 115-128, ISSN: 0277-786X, 2001, XP002326511

- D7: **ZHOU, LANLAN ET AL: "NIR imaging the delivery of cathepsin B probe to breast tumors"**
Proceedings of SPIE-the International Society for Optical Engineering, vol. 4955, pages 505-512, ISSN: 0277-786X, 2003, XP002326513
& OPTICAL TOMOGRAPHY AND SPECTROSCOPY OF TISSUE V
- D8: **KANG, H. W. ET AL: "Targeting of MPEG-protected polyamino acid carrier to human E-selectin in vitro"**
Amino Acids, vol. 23, no. 1-3, pages 301-308, ISSN: 0939-4451, 2002, XP002326512
- D9: **GARCIA-VELASCO JUAN A ET AL: "Interleukin-8 stimulates the adhesion of endometrial stromal cells to fibronectin"**
FERTILITY AND STERILITY, Vol. 72, no. 2, August 1999 (1999-08), pages 336-340, XP002326518 ISSN: 0015-0282
- D10: **MOON WOO KYUNG ET AL: "Enhanced tumor detection using a folate receptor-targeted near-infrared fluorochrome conjugate."**
Bioconjugate Chemistry, vol. 14, no. 3, 1 May 2003 (2003-05-01), pages 539-545, XP002326517 ISSN: 1043-1802
- D11: **MALIK E ET AL: "Angiogenic activity of fluorescent peritoneal fluid in patients with endometriosis"**
Geburtshilfe Und Frauenheilkunde, vol. 59, no. 12, December 1999 (1999-12), pages 622-625, XP008045889 ISSN: 0016-5751
- D12: **KATS ROUSLAN ET AL: "Macrophage migration inhibitory factor is markedly expressed in active and early-stage endometriotic lesions."**
The Journal of Clinical Endocrinology and Metabolism, vol. 87, no. 2, February 2002 (2002-02), pages 883-889, XP002326519 ISSN: 0021-972X

Document D1 discloses the detection of endometriosis by fluorescence after administration of 5-ALA. This compound is converted to protoporphyrin IX in a higher efficiency than in normal tissue, thus allowing for the detection of endometriotic lesions. Document D2 discloses a conjugate of an antibody to a dye, for detecting inter alia

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endometriosis.

Document D3 discloses a conjugate of folate and a fluorescent marker. Such a conjugate is also described in present example 1, and therefore falls within the scope of what is presently claimed.

Document D4 discloses in examples 9-10 the conjugate PF4 - fluorescein. PF4 targets angiogenesis, mentioned specifically in present claim 5 as a target for imaging endometriosis. According to the document, too, this conjugate allows for imaging of endometriosis: see the passage on page 1, lines 24-28.

Document D5 discloses claims the conjugate of a fluorochrome with a compound "selected from the group consisting of glucose, deoxyglucose, L-dopa, dopamine, thymidine, methionine, estradiol, acetate, raclopride, methyldiphosphonate, folate, a long-chain fatty acid, misonidazole, and a therapeutic compound". In the description, the same dye Cy5.5 as in the present application is linked to folate. The claims also specifically mention estradiol as targeting agent.

Document D10 discloses the conjugate of folate to a fluorescent dye.

These documents sufficiently describe the optical imaging agent as presently claimed. In some of these documents, the targeting agent is even the same as in the examples of the present application. Therefore, in view of these documents, the present application does not meet the requirements of Article 33.2 PCT for novelty.

More generally speaking, contrast agents which target angiogenesis, characteristic for *inter alia* endometriosis, but also for (pre)cancerous lesions, have been amply described in the prior art. As additional documents which illustrate this, the present authority further cites the following documents:

Document D6 discloses the conjugate of anti-EGFR-MoAb to Cy5.5. EGFR is expressed in many pre-cancerous lesions.

Document D7 discloses a fluorescent substrate for cathepsin B. This enzyme is expressed in fibrosarcoma HT1080. The fluorescent dye used is, like in the present application, Cy5.5.

Document D8 discloses the same dye as used in the present application, Cy5.5, attached through a polymer linkage to an antibody targeting angiogenesis. However, the experiments are performed *in vitro*.

Document D9 discloses the role of IL-8 in the pathogenesis of endometriosis. It also describes the intracellular conversion of calcein-AM to a fluorescent dye, used to detect

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endometrial cells.

Document D11 discloses the detection of fluorescence of the peritoneal fluid in endometriosis patients after administration of 5-ALA.

Insofar as certain specific conjugates of a targeting agent and a fluorochrome may meet the requirements of Article 33.2 PCT for novelty, such conjugates should demonstrate an inventive step over the agents, which in the prior art are taught to target endometriosis. In the present application, however, the examples only describe the synthesis of 4 specific agents. On the other hand, in the prior art documents, several agents are used to detect endometrial tissue, either *in vitro* or *in vivo*. Therefore, as the level of disclosure of the present application seems to be less than in the prior art, the requirements of Article 33.3 PCT for inventive step have not been met.

3 CLAIMS 2-12

Dependent claims 2-12 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of novelty and/or inventive step (Article 33(2) and (3) PCT).

Re Item VIII.

Claims 1-12, as well as the claims which depend from these, do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The claims attempt to define the subject-matter in terms of the result to be achieved (with/having affinity for an abnormally expressed biological target associated with endometriosis; detectable *in vivo* optical imaging), which merely amounts to a statement of the underlying problem, without providing the technical features necessary for achieving this result.